The opinion in support of the decision being entered today
is *not* binding precedent of the Board.

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte GEORGE H. YOO

Appeal 2007-2864
Application 10/747,798
Technology Center 1600

Decided: September 24, 2007

Before ERIC GRIMES, LORA M. GREEN, and RICHARD M. LEBOVITZ, *Administrative Patent Judges*.

GREEN, *Administrative Patent Judge*.

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. § 134 from the Examiner's final rejection of claims 1-29, 31-33, and 38-60. We have jurisdiction under 35 U.S.C. § 6(b). Claims 1 and 31 are representative of the claims on appeal, and read as follows:

1. A method of inhibiting the growth of a papillomavirus-transformed cell in a hyperplastic lesion in a subject comprising topically administering to said lesion a growth inhibiting amount of a composition comprising (a) an expression cassette comprising a promoter, active in cells of said lesion, operably linked to a polynucleotide encoding a p53 polypeptide, and (b) a pharmaceutical preparation suitable for topical delivery, wherein expression of said p53 polypeptide inhibits growth of said cell.

31. A mouthwash for inhibiting the growth of a papillomavirus transformed cell in a hyperplastic lesion in a subject comprising (a) an expression cassette comprising a promoter operably linked to a polynucleotide encoding a p53 polypeptide, (b) a liquid carrier formulated for oral delivery, and (c) a flavorant.

The Examiner relies upon the following references:

Nielsen	2001/0044420	Nov. 22, 2001
El-Deiry	WO 99/66946	Dec. 29, 1999
Zhang	WO 00/29024	May 25, 2000

Clayman, G. "Clinical protocol for wild type p53 gene induction in premalignancies of squamous epithelium of the oral cavity via an adenoviral vector," PowerPoint presentation, March 2001.

Oda et al. "Chromosomal abnormalities in HPV-16-immortalized oral epithelial cells," *Carcinogenesis*, vol. 17, pp. 2003-2008 (1996).

Flaitz et al. "Molecular piracy: the viral link to carcinogenesis," *Oral Oncol.*, vol. 34, pp. 448-453 (1998).

Recombinant DNA Advisory Committee, Minutes of Meeting March 8, 2001, U.S. Dept. of Health and Human Services ("RAC").

Kaghad et al. "Monoallelically expressed gene related to p53 at 1p36, a region frequently deleted in neuroblastoma and other human cancers" *Cell*, vol. 90, pp. 809-819 (1997).

Hay, D. "Management of oral problems associated with cancer treatment: radiotherapy," www.8.co.nz/hospitaldenistry/papers/Management_of_Oral_Problems_Associated_with_005.htm, accessed by PTO on 10/11/06.

Lowe, B. "Abnormal Cervical Smears – a patient's guide," www.medic8.com/healthguide/articles/abnormalcervicalsmear.html, accessed by PTO on 10/11/06.

"What is a dermatologist?" www.aad.org/public/Parentskids/KidsConnection/Whatisderm.htm, accessed by PTO on 10/11/06.

We affirm.

BACKGROUND

According to the Specification,

> Many proliferative conditions are known to be associated with papillomaviruses. Examples include benign lesions such as cutaneous warts and anogenital warts and premalignant lesions such as epidermodysplasia verruciformis. Papillomaviruses are also associated with malignant lesions including carcinomas of the head and neck, cervix, anus, and penis. In 1998, the American Cancer Society estimated that 60,000 Americans would be diagnosed with head and neck cancer. HPV has been linked to 15-46% of cases and head and neck squamous cell carcinoma (HNSCC). Patients with early stage HNSCC or patients who are cured from advanced cancers have a low probability of death from their primary cancer but have a significant chance of dying from a second primary tumor. More importantly, treatment (chemoprevention) of high-risk populations may reduce the development of a second primary tumor and therefore significantly improve survival. Two chemoprevention trials using 13-cis-retinoic acid (CRA) have demonstrated the efficacy of clinically reversing premalignant lesions and reducing the risk of secondary primary tumors. However, CRA is toxic, poorly tolerated and loses its preventative effects after discontinuation of therapy.

(Specification 2-3 (references omitted).)

Thus, as set forth in the "Summary of the Invention," one of the objects of the invention is to inhibit "the growth of a papillomavirus-transformed cell in a hyperplastic lesion in a subject by topically administering to the subject a composition comprising (a) an expression cassette comprising a promoter, active in the cells of the lesion, operably linked to a polynucleotide encoding a p53 polypeptide, and (b) a pharmaceutical preparation suitable for topical delivery, wherein expression of the p53 polypeptide inhibits growth of the cell." (*Id.* at 4)

As set forth by the Specification,

> A "papillomavirus-transformed cell" is defined as a cell wherein there has been transfer of genetic information from the papillomavirus into the cell. Thus, for instance, a squamous epithelial cell containing papillomavirus genetic material in the nucleus is a papillomavirus-transformed cell. The cell can be a keratinocyte, an epithelial cell, a skin cell, a mucosal cell, or any other cell that can undergo transformation by a papillomavirus. The papillomavirus-transformed cell may express the E6 and E7 HPV products. The hyperplastic lesion can be a squamous cell hyperplastic lesion, a premalignant epithelia lesion, a psoriatic lesion, a cutaneous wart, a periungual wart, an anogenital wart, epidermodysplasi verruciformis, an intraepithelial neoplastic lesion, a focal epithelial hyperplasia, a conjunctival papilloma, a conjunctival carcinoma, a squamous carcinoma, or any pathologic change in tissue which demonstrates wherein there is an increase in the number of cells. In a specific embodiment, the papillomavirus is a human papillomavirus.

(*Id.* at 4-5.)

Moreover,

> Head and neck cancers can arise from squamous cell carcinomas (SCC), which are the second most common form of skin cancer. They occur in men more often than women and originate primarily in skin exposed to the sun in a dose-dependent manner. SCCs are likely derived from keratinocytes located near the skin surface. Aneuploidy is common in this type of cancer, as is the presence of *p53* mutations. SCC may occur anywhere on the skin, although it may arise on the mucosal membranes of the mouth, nose, lips, throat, eyelids, lining of the breathing tubes, anus, cervix, *etc.*

(*Id.* at 42)

DISCUSSION

Claims 1-12, 15, 18, 23-28, 33, 38-48, 51 and 54 stand rejected under 35 U.S.C. § 102(a) as being anticipated by Clayman as evidenced by Oda and Flaitz. As Appellant does not argue claims 2, 3, 5, 7-12, 15, 18, 23-28, 38-48, and 51 separately from claim 1, those claims stand or fall with claim 1. 37 C.F.R. § 41.37(c)(1)(vii) (2006).

Clayman is relied upon for describing

> a clinical protocol for treating humans with premalignancies of squamous epithelium in the oral cavity with an adenoviral vector encoding p53 under control of the CMV promoter by intramucosal injection in the area of the lesion followed by topical application of a mouthwash comprising the vector (see pages 4-6 especially).

(Answer 5.)

According to the Examiner, Clayman does not specifically teach that papilloma virus infection would be present in the cells of the lesion, but that characteristic "is inherent in a substantial fraction of patients that would be the target of the disclosed treatment." (*Id.*) Oda is cited for teaching that up

to 90% or oral cancers have been reported as having HPV DNA, and Flaitz is cited for teaching that about one-half of oral epithelial dysplasias are infected with HPV, and that between one-third and one-half of oral squamous cell carcinoma involves HPV infection (*id.*). Thus, the Examiner finds that "one of skill in the art of oral cancer would have been aware that the treatment of Clayman would necessarily involve treatment of hyperplastic lesions that comprise HPV infected cells in a substantial fraction of target patients." (*Id.*)

With respect to claims 18, 33, and 54, which require that the composition be formulated as a douche, the Examiner asserts that "a douche is simply a jet of liquid applied to a part of the body; so a douche solution is simply liquid." (*Id.*)

In order for a prior art reference to serve as an anticipatory reference, it must disclose every limitation of the claimed invention, either explicitly or inherently. *In re Schreiber*, 128 F.3d 1473, 1477, 44 USPQ2d 1429, 1432 (Fed. Cir. 1997). We find that Clayman discloses every limitation of the claimed subject matter. Therefore, the rejection of claims 1-12, 15, 18, 23-28, 33, 38-48, 51 and 54 is affirmed.

Appellant argues that the Examiner has not established that in practicing the Clayman method one is inherently practicing the claimed invention (Br.[1] 5). According to Appellant, Oda in fact teaches that a substantial fraction of oral and cervical cancers are not infected with HPV (*id.* at 6). Appellant asserts:

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[1] All references to the Brief (Br.) are to the Supplemental Brief on Appeal, dated August 23, 2006.

> The present invention is not directed to obtaining patent protection of a method of inhibiting the growth of cells that are not infected with HPV. That the claimed method might be applied in the treatment of cells not infected by HPV is not relevant to the issue of whether Clayman anticipates the claimed invention. The issue is whether it would be inherent that every cancer set forth in Clayman would be infected with HPV. Clayman provides no explicit teaching. In fact, Oda and Flaitz support the notion that it is NOT inherent that every cancer set forth in Clayman would be infected with HPV.

(*Id.*) Appellant cites *MEHL/Biophile Int'l Corp. v. Milgraum*, 192 F.3d 1362, 1365 (Fed. Cir. 1999), for the proposition that inherency is not established by probabilities or possibilities, and that occasional results are not inherent (Br. 7). Thus, Appellant asserts, "the mere possibility that one of the lesions set forth in Clayman might contain HPV DNA is not sufficient to establish inherent anticipation." (*Id.*)

Appellant essentially appears to be arguing that as Oda and Flaitz do not teach that every malignancy of the cervix or oral cavity involves cells that are infected with HPV, Clayman cannot anticipate the claimed subject matter. That is not the standard, however, by which anticipation is determined.

Inherent anticipation does not require intent or recognition that a prior art process achieve a result which is claimed. "Inherency is not necessarily coterminous with the knowledge of those of ordinary skill in the art. Artisans of ordinary skill may not recognize the inherent characteristics or functioning of the prior art." *MEHL/Biophile*, 192 F.3d at 1365, 52 USPQ2d at 1305-06.

As noted by the Examiner, Clayman teaches a clinical protocol for treating humans with premalignancies of squamous epithelium in the oral

cavity with an adenoviral vector encoding p53 under control of the CMV promoter by intramucosal injection in the area of the lesion followed by topical application of a mouthwash comprising the vector. The record establishes by a preponderance of the evidence that human papilloma virus infection is known to be associated with different cancerous and precancerous conditions, such as the premalignancies of the squamous epithelium as taught by Clayman. *See, e.g., Ethicon, Inc. v. Quigg*, 849 F.2d 1422, 1427, 7 USPQ2d 1152, 1156 (Fed. Cir. 1988) (explaining the general evidentiary standard for proceedings before the Office); *In re Kollar*, 286 F.3d 1326, 1329, 62 USPQ2d 1425, 1427 (Fed. Cir. 2002) ("The PTO bears the initial burden of demonstrating that the preponderance of the evidence establishes, *prima facie*, facts supporting the conclusion that the claimed invention was on sale within the meaning of § 102(b).").

As acknowledged in the Specification at page 2, "[m]any proliferative conditions are known to be associated with papillomaviruses. Examples include benign lesions such as cutaneous warts and anogenital warts and premalignant lesions such as epidermodysplasia verruciformis. Papillomaviruses are also associated with malignant lesions including carcinomas of the head and neck, cervix, anus, and penis." El-Deiry teaches that "HPV infection is well-known to result in cancers of the uterine cervix. In addition to anogen[it]al cancer, HPV infection may also result in esophageal squamous cell cancer, laryngeal papilloma, bronchiolo-alveolar carcinoma, penile carcinoma and bladder carcinoma, among others." (El-Deiry, p. 14.) Further, as noted by the rejection, Oda teaches that up to 90% of oral cancers have been reported as having HPV DNA, and teaches that about one-half of oral epithelial dysplasias are infected with HPV, and that

between one-third and one-half of oral squamous cell carcinoma involves HPV infection. Moreover, although not disclosing the results, Clayman did test for HPV of the microdissected lesion (Slide 8 entitled "Special Protocol Testing Summary Pre Treatment"). Thus, in those lesions in which HPV is involved, the growth of a papillomavirus-transformed cell would be inhibited. It is unnecessary that this result was intended or recognized.

It may be that not every instance in which the claimed composition is administered by Clayman to a hyperplastic lesion would result in anticipation. But, as discussed above, HPV involvement is common in such lesions, establishing that anticipation would necessarily result. In *Perricone v. Medicis Pharm. Corp.*, 432 F.3d 1368, 1379, 77 USPQ2d 1321, 1328 (Fed. Cir. 2005), a claim to a method of preventing sunburn damage by topically applying a composition to exposed skin was held to be anticipated by a disclosure of a topical skin cream "because all skin surfaces are susceptible to sunburn damage." Anticipation was based on the skin's *susceptibility* to sunburn, not the requirement that, each time the prior art topical cream was applied to exposed skin, sunburn was actually prevented. Likewise, we do not find it necessary that HPV involvement be present in every case. It is enough that human papillomavirus infection is known to be associated with different cancerous and precancerous conditions. Thus, the result would not be "occasional," but a certainty in a certain percentage of patients being treated using the composition required by the claimed method.

Appellant argues as to claim 4 that Clayman does not expressly or inherently disclose the limitation "wherein the cell is a keratinocyte." (Br. 8.)

As noted by the Examiner, citing Flaitz at page 452, column 1, (Answer 11), "squamous cells are keratinocytes, and HPV is trophic for squamous cells and is capable of replication only in squamous cells." Appellant responds that most of the oral cavity is lined by nonkeratinized squamous epithelium, and not keratinocytes, and that "[b]ecause squamous cells are not necessarily keratinocytes, there is no inherent anticipation." (Reply Br. 5.)

Appellant has provided no evidence to rebut Flaitz to support the assertion that most of the oral cavity is lined by nonkeratinized squamous epithelium, and arguments of counsel cannot take the place of evidence in the record. *In re Scarbrough*, 500 F.2d 560, 566, 182 USPQ 298, 302 (CCPA 1974). In addition, we also cite the Online Merck Manual, Home Edition,[2] for its teaching that "[s]quamous cells (keratinocytes) are the main structural cells of the epidermis. Squamous cell carcinoma usually develops on sun-exposed areas but may grow anywhere on the skin or in the mouth, where sun exposure is minimal." Thus, we find that keratinocytes would be present on the inside of the mouth, and thus, the method of Clayman, which requires topical application of a mouthwash, anticipates claim 4.

As to claim 6 which further limits the papillomavirus-transformed cell to a skin cell, Appellant argues that Clayman pertains to the treatment of the oral cavity, which is not lined by skin cells (Br. 8).

Our mandate is to give claims their broadest reasonable construction. *In re American Academy of Science Tech Center*, 367 F.3d 1359, 1364, 70 U.S.P.Q.2d 1827, 1830 (Fed. Cir. 2004). "An essential purpose of patent

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[2] www.merck.com/mmhe/sec18/ch216/ch216c.html, accessed September 14, 2007.

examination is to fashion claims that are precise, clear, correct, and unambiguous. Only in this way can uncertainties of claim scope be removed, as much as possible, during the administrative process." *In re Zletz*, 893 F.2d 319, 322 (Fed. Cir. 1989).

The Examiner cites Hay (first sheet); Lowe (first sheet); and "What is a Dermatologist?" (third sheet), to support the interpretation of skin as including the mucosa of the mouth and cervix (Answer 12). Appellant responds that the Specification supports a plain and ordinary meaning of skin distinct from mucosa. For example, Appellant cites page 3, lines 25-26, which teaches that the "cell can be a keratinocyte, an epithelial cell, a skin cell, a mucosal cell, or any other cell that can undergo transformation by a papillomavirus." That teaching from the Specification, however, does not support Appellant's assertion that the cells are mutually exclusive. For example, an epithelial cell may also be a skin cell.[3] Thus, we find that the preponderance of the evidence supports the Examiner's proffered interpretation of the term "skin," and the rejection of claim 6 is affirmed.

As to claim 18, 33, and 54, Appellant argues that Clayman cannot anticipate these claims as there is no express or inherent disclosure of the claimed "douche solution." (Br. 8.) Appellant also asserts that contrary to the Examiner's argument that a douche is simply a jet of liquid, "there is no disclosure in Clayman pertaining to any *jet of liquid* applied to any part of the body, vagina or otherwise." (*Id.* (emphasis in original).)

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[3] The American Heritage Science Dictionary defines the epithelium as lining the outer layer of the skin (epidermis), as well as the surface of most body cavities. (epithelial, Dictionary.com. *The American Heritage® Science Dictionary*. Houghton Mifflin Company. dictionary.reference.com/browse/epithelial (accessed: September 14, 2007)).

Claim 18 is drawn to the method of claim 1, wherein the composition is formulated as a douche solution. Note that claim 18 does not require the use of the solution as a douche, but merely for the composition to be formulated as a douche solution. Thus, we agree that the composition of Clayman, which comprises the vector in a liquid that can be swished in the mouth, could also be used as a douche. Moreover, we also find that Appellant has not presented any evidence to contradict that finding, and the rejection is affirmed as to claims 18, 33, and 54.

As to claim 33, Appellant also argues that there "is no indication in Clayman that any of the liquid formulations set forth therein are suitable for vaginal delivery," and that "the Examiner has cited no evidence to establish that any liquid carrier set forth in Clayman is a carrier formulated for vaginal delivery." (Br. 9.)

Claim 33 is drawn to "[a] douche solution for inhibiting the growth of a papillomavirus-transformed cell in a hyperplastic lesion in a subject comprising (a) an expression cassette comprising a promoter operably linked to a polynucleotide encoding a p53 polypeptide, and (b) a liquid carrier formulated for vaginal delivery." As discussed above, we agree with the Examiner that the composition of Clayman, which comprises the vector in a liquid that can be swished in the mouth, could also be used as a douche. Thus, the rejection of claim 33 is affirmed.

Claims 1-12, 15, 18, 23-28, 33, 38-48, 51, and 54 stand rejected under 35 U.S.C. § 102(b) as being anticipated by RAC as evidenced by Oda and Flaitz.

> RAC is relied upon for describing
>
> a clinical protocol for treating humans with premalignancies of squamous epithelium in the oral cavity with an adenoviral vector encoding p53 under control of the CMV promoter by intramucosal injection in the area of the lesion followed by topical application of a mouthwash comprising the vector (see pages 10-11 especially).

(Answer 6.)

As with the prior rejection, the Examiner notes that RAC does not disclose papillomavirus infection of the cells in the lesion (*id.*). The Examiner relies of Oda and Flaitz as set forth in the rejection above (*id.*). The Examiner asserts therefore "one of skill in the art of oral cancer would have been aware that the treatment of Clayman described in RAC would necessarily involve treatment of hyperplastic lesions that comprise HPV infected cells." (*Id.*)

With respect to claims 18, 33, and 54, which require that the composition be formulated as a douche, the Examiner asserts that "a douche is simply a jet of liquid applied to a part of the body; so a douche solution is simply liquid." (*Id.*)

Appellant essentially reiterates his arguments as to the rejection of claims 1-12, 15, 18, 23-28, 33, 38-48, 51, and 54 under 35 U.S.C. § 102(a) as being anticipated by Clayman as evidenced by Oda and Flaitz (Br. 10-11). Thus, this rejection is affirmed for the reasons already set forth with respect to that rejection.

Appellant also reiterates his arguments as to claims 4, 6, 18, 33, and 54, and the rejection of those claims is also affirmed for the reasons set forth above.

Claims 1-14, 19-29, 38-50, and 55-60 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Nielsen as evidenced by Oda and Flaitz. As Appellant does not argue claims 2, 3, 5, 7-14, 19-29, 38-50, and 55-60, separately, they stand or fall with claim 1.

Neilsen is relied upon for teaching

> the treatment of cancer in general, including cervical cancer and head and neck cancer, by a combination of p53 gene therapy and gemcitabine chemotherapy. The p53 gene can be delivered by non-viral lipid-based plasmid delivery or by delivery in a viral vector based on adenovirus, AAV, retrovirus, or vaccinia virus. The p53 coding sequence in the vector may be under control of a constitutive or tumor specific promoter. Nielsen discloses topical delivery of the vector to the location of a tumor, including to the surgical wound resulting from tumor resection. Pharmaceutical compositions comprising the vector include compositions for transmucosal or transdermal delivery for treatment of tumors in the mouth, nasal mucosa, vagina and uterus are disclosed. Disclosed compositions include emulsions (i.e. cream, ointment or salve), aerosols, tablets, lozenges and suppositories.

(Answer 7.)

Appellant essentially reiterates his arguments as to the rejection of claims 1-12, 15, 18, 23-28, 33, 38-48, 51, and 54 under 35 U.S.C. § 102(a) as being anticipated by Clayman as evidenced by Oda and Flaitz (Br. 11-12). Thus, the rejection as to claims 1-3, 5, 7-14, 19-29, 38-50, and 55-60 is affirmed for the reasons set forth with respect to that rejection.

As to claims 4 and 6, Appellant argues that Neilsen cannot anticipate claims 4 and 6 because "it does not expressly or inherently disclose 'a keratinocyte,' (claim 4), or 'a skin cell' (claim 6)." (Br. 12.) Appellant's attention is directed to the response to the arguments with respect to the

rejection under § 102(a) over Clayman. In addition, Neilsen teaches transdermal delivery, which would be through the skin, and thus, Neilsen does disclose treatment of a keratinocyte and a skin cell.

Claims 1-15, 18-29, 33, 38-51, and 54-60 stand rejected under 35 U.S.C. § 102(b) as being anticipated by El-Deiry.

The Examiner first cites the definition of p53 found at page 14 of the Specification, which states that "the term 'p53' is intended to refer to the exemplified p53 molecules as well as all p53 homologues from other species." (Answer 8.) The Examiner notes that El-Deiry relates to gene therapy with a transgene of p73, which El-Deiry specifically states is a homolog of p53 (*id.*). The Examiner thus concludes that given the definition of p53 in the Specification, p53 as used in the claims encompasses p73 as taught by El-Deiry (*id.*).

El-Deiry is cited by the Examiner for teaching

> the treatment of cells transformed by infection with a papilloma virus, such as HPV, particularly those in certain types of cancer involving papilloma virus infection, e.g. cervical cancer, esophageal squamous cell cancer, laryngeal papilloma, bronchio-alveolar carcinoma, penile carcinoma and bladder carcinoma. El-Deiry teaches methods of treating such cells *in vivo* by gene therapy with a vector that expresses p73, including by topical delivery. The vector may be a liposomal vector or a viral vector based on a retrovirus, adenovirus, and AAV. The p73 coding sequence is under control of a constitutive promoter or papilloma virus-regulated promoter. The pharmaceutical composition comprising the vector may also include a chemotherapeutic agent, and can be formulated as an aerosol for inhalation, in a lotion or suppository, in a liquid for oral delivery, or in a transdermal patch, and used such that the composition contacts the target cells. See entire document, especially page 1, lines 8-12 and 20-22; page 3, line 10, to page 5, line 7; pages 12-16; pages 20-23; page 24, line 33 to page 25,

> line 31. With respect to timed-release formulations, formulations such as creams, ointments, tablets, suppositories, etc. release their contents as the carriers break down over time, and so are timed-release.

(*Id.* at 8-9.)

Appellant argues that "El-Deiry does not anticipate the claimed invention because it does not expressly or inherently disclose administration of a polynucleotide encoding a p53 polypeptide to a papillomavirus-transformed cell." (Br. 12.) According to Appellant "p53" is intended to refer to the exemplified p53, which is human p53, as well as p53 from another species, such as a mouse (*id.* at 13). Appellant argues that "in contrast, El-Diery teaches that p73 is structurally and functionally dissimilar to p53. For example, El-Deiry indicates that unlike p53, p73 is not targeted for degradation in Ad-E6 infected cancer cells." (*Id.*)

Page 14 of the Specification states that "[t]hroughout this application, the term 'p53' is intended to refer to the exemplified p53 molecules as well as all p53 homologues from other species." (Specification 14.) As set forth by Appellant, the exemplified p53 is human (Br. 13). We thus agree with Appellant that "[o]ne of ordinary skill in the art would understand that if the exemplified p53 molecule was a human p53, then in the context of the present specification, 'all p53 homologues from other species' refers to p53 molecules from species other than human p53. Thus, the ordinary artisan would understand that 'p53' as used in the present specification refers to human p53 and p53 molecules from other species." (Reply Br. 9-10.) The rejection as to El-Deiry, who teaches the use of a p73 protein that is endogenous to the species being treated, such as a human (El-Deiry at p. 15), is thus reversed.

Claims 16, 17, 31, 32, 52, and 53 stand rejected under 35 U.S.C. § 103(a) as being obvious over RAC as evidenced by Oda and Flaitz, or El-Deiry, as further combined with Zhang. The rejection, to the extent it is based on El-Deiry and Zhang, is reversed for the reasons discussed above.

RAC is relied upon as above (Answer 9). According to the Examiner, RAC describes "liquid compositions for oral delivery of the vector, but [does not] describe inclusion of a flavorant in the composition." (*Id.*)

Zhang is relied upon for teaching oral pharmaceutical compositions comprising an adenoviral vector, wherein the composition may include a flavorant (*id.*). The Examiner concludes that it would have been obvious to include a flavorant, such as peppermint or wintergreen oil, in the oral pharmaceutical compositions of RAC as the inclusion of a flavorant improves the palatability of the composition.

"In rejecting claims under 35 U.S.C. § 103, the examiner bears the initial burden of presenting a prima facie case of obviousness. Only if that burden is met, does the burden of coming forward with evidence or argument shift to the applicant." *In re Rijckaert*, 9 F.3d 1531, 1532, 28 USPQ2d 1955, 1956 (Fed. Cir. 1993) (citations omitted). In order to determine whether a prima facie case of obviousness has been established, we consider the factors set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1996): (1) the scope and content of the prior art; (2) the differences between the prior art and the claims at issue; (3) the level of ordinary skill in the relevant art; and (4) objective evidence of nonobviousness, if present.

Appellant argues that the Examiner has failed to establish a prima facie case of obviousness as Zhang fails to remedy the deficiencies of RAC (Br. 15-16). Appellant's argument is not found to be convincing as we have

already found that RAC anticipates the subject matter of claims 1-12, 15, 18, 23-28, 33, 38-48, 51, and 54.

Appellant argues further that the Examiner has failed to set forth any suggestion or motivation for the combination (Reply Br. 11). Specifically, Appellant argues that "the claims at issue are directed to inhibiting, suppressing or preventing growth of papillomavirus-transformed cells in a hyperplastic lesion. No specific motivation to provide for inhibiting, suppressing or preventing growth of a papillomavirus-transformed cells in a hyperplastic lesion using a flavorant-containing composition containing p53 . . . has been cited by the Examiner." (*Id.* at 12)

RAC teaches topical application of a mouthwash comprising the vector, and Zhang teaches that an oral pharmaceutical composition comprising an adenoviral vector may include a flavorant. Thus, we agree with the Examiner that it would have been obvious to include a flavorant as taught by Zhang in the mouthwash of RAC. *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1742, 82 USPQ2d 1385, 1397 (2007) ("One of the ways in which a patent's subject matter can be proved obvious is by noting that there existed at the time of the invention a known problem for which there was an obvious solution encompassed by the patent's claims.")

CONCLUSION

As the Examiner has established a prima facie case of unpatentability as to all the claims on appeal, the Examiner is affirmed.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a)(1)(iv) (2006).

AFFIRMED

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